

PATENT SPECIFICATION

NO DRAWINGS

Inventors: DALE RICHARD HOFF and MICHAEL HERBERT FISHER

1.198.941

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Date of Application and filing Complete Specification: 1 Feb., 1968.

No. 5259/68.

Application made in United States of America (No. 613746) on 3 Feb., 1967.

Application made in United States of America (No. 696496) on 9 Jan., 1968.

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Index at acceptance: —C2 C(1Q2, 1Q6C, 1Q7A, 1Q7B, 1Q8A, 1Q9A, 1Q11G, 2A3, 2A13, 2C4, 2C7I, 2C7C, 2C7E, 2C7F, 2D45, 2R15, 200, 202, 213, 215, 22Y, 220, 222, 225, 226, 246, 247, 25Y, 250, 251, 252, 253, 254, 255, 256, 28X, 29Y, 29X, 30Y, 31Y, 313, 315, 32Y, 321, 332, 338, 339, 34Y, 340, 341, 342, 351, 355, 36Y, 36X, 366, 367, 368, 45Y, 453, 470, 471, 577, 578, 579, 601, 603, 604, 610, 62X, 624, 626, 627, 652, 661, 662, 669, 670, 671, 672, 681, 708, 71Y, 72Y, 72X

PATENTS ACT, 1949

SPECIFICATION NO. 1,198,941

In pursuance of Section 3 of the Patents Act 1949, the Specification has been amended in the following manner:—

Page 1, after line 59, insert 'It should be noted that when x is oxygen, R₃ is hydrogen and R₄ is a radical of formula RO-, then R₁ is not a pyrazolyl radical.'

Page 15, delete lines '119, 120, 121 and 122'

Page 16, delete lines '1, 2, 3 and 4'

Page 16, line 5, delete 'Example 85'

Page 16, for Examples '86 to 94' read '85 to 93'

Page 17, line 10, after 'radical' delete full stop insert ', with the proviso that when x is oxygen, R₃ is hydrogen and R₄ is a radical of formula RO-, then R₁ is not a pyrazolyl radical.'

THE PATENT OFFICE
8 February 1972

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International Classification: —C 07 d 99/02

COMPLETE SPECIFICATION

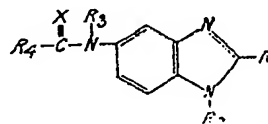
Benzimidazole Derivatives

We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with benzimidazoles having a heteroaryl radical at the 2-position and a substituted amino radical at the 5-position. The 5-substituent is of the carbamate, thionocarbamate, carbonylamino or thiocarbonylamino type. The invention is also concerned with processes for making such compounds, anthelmintic compositions containing them as the essential active ingredients and methods of treating helminthiasis in non-human animals by using the new compounds.

Benzimidazoles having a heteroaryl radical in the 2-position have previously been proposed as anthelmintic agents. Although these materials are active anthelmintic agents, the search has continued for substances which are more potent and which are effective against helminths that are non-responsive or weakly responsive to the prior art compounds.

The novel benzimidazoles provided in accordance with the present invention have the following structural formula:



or are non-toxic acid-addition salts or heavy metal complexes of such compounds in which R_2 is hydrogen. In the above formula, the symbol R_1 represents a five-membered monocyclic heteroaromatic ring containing from 1 to 3 of the hetero atoms, oxygen, sulfur and nitrogen. The symbol R_3 in the above formula represents a hydrogen atom or a straight or branched chain C_{1-8} alkyl group, for example, methyl, ethyl, propyl, isopropyl, amyl, hexyl or n-octyl. The symbol X in the above formula represents oxygen or sulfur.

The symbol R_1 in the foregoing Formula I represents a hydrogen atom, an aralkyl, haloaralkyl, cycloalkyl, C_{1-8} alkylamino, di(C_{1-8} alkyl)amino, cycloalkylamino, alkylidenimino or hetero-interrupted alkylidenimino radical, or a radical of formula $R-$, $RO-$ or $RS-$, in which R is a C_{1-8} univalent aliphatic hydrocarbon, C_{1-8} univalent aliphatic haloalkyl, aryl, heterocyclic, haloaryl, alkaryl or aminoaryl radical. Compounds in which R_1 is in the form $RO-$ or $RS-$ give carbamates or thionocarbamates at the 5-position; the other compounds give a 5-substituent of the carbonylamino or thiocarbonylamino type.

[Price

5 R_2 in the foregoing formula represents a hydrogen atom or a hydroxy, C_{1-8} alkoxy, C_{1-8} alkyl, aralkyl, acyl, acyloxy, carboxy- (C_{1-8} alkoxy), carbamoyl, N-alkylcarbamoyl or alkoxycarbonyl radical.

10 Specific examples of the heteroaromatic substituents represented by R_1 in Formula I are five-membered rings containing nitrogen, sulfur or oxygen as the sole hetero atom, e.g. furyl, thienyl, pyrazolyl, imidazolyl and pyrrol; five-membered rings containing nitro-
15 gen and sulfur, e.g. thiazolyl, thiadiazolyl, and isothiazolyl; and five-membered rings contain- ing nitrogen and oxygen, such as oxazolyl. The nitrogen-and-sulfur-containing hetero-
cycles are the preferred substituents with 4'-thiazolyl and 2'-thiazolyl being particularly desirable.

20 Examples of R_1 include straight or branched-chain C_{1-8} alkoxy, C_{1-8} haloalkoxy and C_{2-8} alkenoxy radicals, such as methoxy, ethoxy, isopropoxy, allyloxy, propenyloxy, 2,2,2 - trifluoroethoxy, amyloxy and n - octyloxy, straight or branched chain C_{1-8} alkylthio C_{1-8} haloalkylthio and C_{2-8} alkenyl-
25 thio radicals, such as methylthio, ethylthio, 2 - chloroethylthio, isopropylthio, allylthio and n - hexylthio; phenoxy, halophenoxy, amino- phenoxy, tolyloxy, naphthoxy, phenylthio, halophenylthio, aminophenylthio, tolylthio,
30 naphthylthio, furyloxy, thiazolyloxy, thienyl- oxy, pyrazinyloxy, furylthio, thiazolylthio, thienylthio and pyrazinylthio radicals; straight or branched-chain C_{1-8} alkyl, C_{1-8} haloalkyl
35 or C_{2-8} alkenyl radicals such as methyl, dichloromethyl, ethyl isopropyl, allyl, *t*-butyl, amyl and octyl; cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, phenyl, halophenyl, aminophenyl, tolyl, naphthyl, benzyl, halo-
40 benzyl, phenethyl, furyl, thiazolyl, thienyl, pyridyl, methylamino, diethylamino, iso- propylamino, methylethylamino, n - hexyl- amino, piperazino, piperidino, morpholino and pyrrolidino radicals.

45 In the preferred compounds of the inven- tion, R_2 represents hydrogen. However, other values of R_2 apart from those specifically mentioned above are C_{1-8} alkanoyl, C_{1-8} alkanoyloxy, methyl, ethyl, propyl, benzyl, methoxy, ethoxy, n - propoxy, carboxy-
50 methoxy, carboxyethoxy, carboxypropoxy, N-methylcarbamoyl, N-ethylcarbamoyl, N-butyl- carbamoyl, methoxycarbonyl, ethoxycarbonyl and isopropoxycarbonyl.

55 In those compounds in which R_2 is hydro- gen, there may be formed acid-addition salts with inorganic acids such as hydrochloric, sul- furic, nitric, phosphoric and hypophosphorus acids and with organic acids such as acetic,
60 tertiarybutylacetic, dialkylphosphoric, citric, benzoic, lactic and oxalic acids. Certain of these salts are more soluble than the parent base and for this reason are preferred when a soluble form of product is desired. This
65 invention also contemplates the heavy metal

complexes of the disclosed benzimidazoles which are obtained by reacting the benzimida-
zole (where R_2 is hydrogen) with a salt of a heavy metal such as copper, lead, iron and mercury.

70 It has been found that the substituted amino substituent at the 5-position of the benzimidazole nucleus imparts, in many cases, a surprisingly high degree of anthelmintic activity as compared with the corresponding
75 5 - unsubstituted compound which was not predictable or anticipated from the teachings of the prior art. Compounds of this invention are used to treat helminthiasis in the form of orally administrable drenches, boluses, cap-
80 sules, or in animal feeds. They may also be administered to the infected host of intra- muscular, intraruminal or intratracheal in- jection. In addition to their high degree of
85 anthelmintic activity, novel benzimidazoles of this invention also possess significant anti- fungal activity.

90 The preferred compounds are of the car- bamate and carbonylamino type (i.e. those compounds in which X is oxygen), particu- larly those in which, in addition, R_1 is thiazolyl, R_2 and R_3 are both hydrogen and R_4 is methoxy, ethoxy, isopropoxy, benzoyl or
95 *p* - fluorobenzoyl. Compounds of these classes have been found to be specially potent an- thelmintic agents.

100 The novel benzimidazoles of this invention, in which the substituent at the 5-position is of the carbamate or thionocarbamate type, are readily prepared by reacting a 5 - amino - 2 - R_1 - benzimidazole with an R - halo-
formate or halothioformate where R is as de- fined above and R_1 is RO— or RS—. When
105 an R - haloformate is used, the resultant sub- stituent at the 5 - position of the benzimidazole will have the characteristic structure, R—O—CO—NH—. For convenience, such
substituents will be referred to generically as hydrocarbonoxy-carbonylamino radicals. When
110 an R - halothioformate is used as a reactant, the resultant substituent at the 5 - position will have the characteristic structure, R—S—CO—NH—. For convenience, these
substituents will be referred to generically as hydrocarbonthio - carbonylamino radicals.

115 The above reaction is preferably carried out using the appropriate chloroformate or chloro- thioformate. It is conveniently conducted at temperatures of from about 20—50°C in an
120 inorganic solvent and in the presence of an acid-binding agent. It has been found very convenient to conduct the reaction in a sol- vent such as pyridine which also serves as
acid-binding agent, although other basic solvents such as the picolines and lutidines
125 could be used equally well. Neutral solvents, however, can be used, in which case the pro- duct is isolated as the acid - addition salt. The resulting carbamate is water - insoluble
130 and is conveniently precipitated by diluting

the reaction mixture with a relatively large volume of water. The solid is then recovered by standard methods and purified by recrystallization from solvents such as methanol, ethanol, acetonitrile or mixtures thereof. When a lower alkanol is used as the recrystallization solvent, there is a tendency on the part of some of the compounds, especially those in which the radical R_1 is of lower molecular weight, to crystallize as an alcohol solvate. When this occurs, the free compound may be obtained by drying the solvate under vacuum at temperatures of from 60–90°C.

Representative of the compounds within the scope of the invention and prepared by the above-described procedure are 5 - methoxy - carbonylamino - 2 - (4' - thiazolyl)benzimidazole, 5 - ethoxycarbonylamino - 2 - (2' - thiazolyl)benzimidazole, 5 - methylthio - carbonylamino - 2 - (2' - furyl)benzimidazole, 5 - ethylthiocarbonylamino - 2 - (3' - thienyl) - benzimidazole, 5 - *p* - fluorophenoxycarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, 5 - benzyloxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole, 5 - cyclopropyloxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, 5 - thiazolyloxycarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, 5 - phenylthiocarbonylamino - 2 - (2' - oxazolyl) - benzimidazole, and 5 - phenoxycarbonyl - amino - 2 - (4' - pyrrol)benzimidazole.

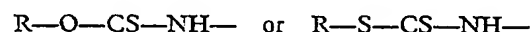
It has been found also that the hydrocarbonoxycarbonylamino compounds of this invention may be prepared directly from the hydrocarbonthio - carbonylamino embodiments by treating the latter in the presence of a weakly basic catalyst such as dibutyltin oxide and aluminium isopropoxide with the alcohol corresponding to the desired R_1 function. Through this ester exchange technique, for example, 5 - cyclopropoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole may be prepared by treating the corresponding 5 - ethylthiocarbonylamino compound with cyclopropanol in the presence of dibutyltin oxide; 5 - phenoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole may be prepared by treating the corresponding 5 - methylthio - carbonylamino compound with phenol in the presence of aluminium isopropoxide; and 5 - benzylcarbonylamino - 2 - (4' - thiazolyl) - benzimidazole may be prepared by treating the corresponding 5 - phenylthiocarbonyl - amino compound with benzyl alcohol in the presence of dibutyltin oxide. While any of the 5 - hydrocarbonthio - carbonylamino embodiments of this invention may be employed as starting material for the ester exchange, it is preferred to use a C_{1-8} alkylthio - carbonylamino compound such as 5 - methyl - 1 - (or ethyl)thiocarbonylamino - 2 - (4' - thiazolyl)benzimidazole.

The reaction is preferably carried out by refluxing the 5 - hydrocarbonthio - carbonyl - amino benzimidazole in the selected alcohol

in the presence of a catalytic quantity of the weak base. Reaction is usually complete in about 10 to about 24 hours after which the 5 - hydrocarbonoxycarbonylamino benzimidazole is recovered by evaporation of the solvent. The residue is purified by conventional recrystallization techniques.

The compounds of this invention having a carbonylamino radical at the 5 - position are also obtained from a 5 - amino - 2 - R_1 - benzimidazole by reacting the benzimidazole with the appropriate acyl halide or an acid anhydride. It has been found convenient to use an acyl chloride as the reactant and carry out the process in an organic solvent such as pyridine, a picoline or a lutidine, which will then also serve as an acid binding agent. The resulting 5 - carbonylamino benzimidazoles are only slightly soluble in water and are conveniently recovered by the same method as that described above for recovering the carbamates. Representative examples of novel benzimidazoles obtained in this fashion are 5 - acetylamino - 2 - (4' - thiazolyl) - benzimidazole, 5 - (*p* - fluorobenzoyl)amino - 2 - (2' - thiazolyl)benzimidazole, 5 - formyl - amino - 2 - (3' - thienyl)benzimidazole, 5 - phenylacetylamino - 2 - (2' - oxazolyl) - benzimidazole, 5 - benzoylamino - 2 - (4' - thiazolyl)benzimidazole and 5 - propionyl - amino - 2 - (4' - thiazolyl)benzimidazole.

The novel benzimidazoles of this invention in which the substituent at the 5 - position is of the thionocarbamate type may be prepared by a variety of methods from starting materials either well known or readily obtainable by the techniques hereinafter described. The thionocarbamate substituent at the 5 - position will have the characteristic structure



where R is the hydrocarbon residue derived from R_1 as defined above. For convenience, thionocarbamates of the structure $R-O-CS-NH-$ may be referred to generically as hydrocarbonoxy - thiocarbonyl - amino compounds and thionocarbamates having the structure $R-S-CS-NH-$ may be referred to generically as hydrocarbonthio - thiocarbonylamino compounds.

The 5 - hydrocarbonoxy - thiocarbonyl - amino benzimidazoles of this invention are readily prepared by treating a 5 - amino - 2 - R_1 - benzimidazole with the appropriate alkoxy, aryloxy, or heteroaryloxy thiocarbonyl halide, preferably the thiocarbonyl chloride. The reaction is conveniently carried out by adding the thiocarbonyl halide at room temperature to a stirred suspension of the amino benzimidazole in a suitable organic solvent such as pyridine. Reaction is usually complete in from 1 to 3 hours after which the product may be precipitated from the reac-

tion mixture by the addition of water. The product is recovered by filtration and purified by conventional recrystallization techniques.

5 The 5 - hydrocarbonoxythiocarbonylamino benzimidazoles of this invention, (and particularly 5 - phenoxythiocarbonylamino benzimidazoles when dissolved in pyridine and heated at about 100°C. for 1 to 4 hours, are converted into the corresponding 5 - iso-

10 thiocyanato benzimidazole which compound is a valuable intermediate in the preparation of many of the novel benzimidazoles of this invention. It has been found, for example, that the 5 - hydrocarbonoxythiocarbonyl -

15 amino benzimidazoles themselves are readily prepared by reacting a 5 - isothiocyanato benzimidazole with an alcohol. Thus, 5 - methoxythiocarbonylamino - 2 - (4' - thiazolyl)benzimidazole may be prepared by

20 treating 5 - isothiocyanato - 2 - (4' - thiazolyl)benzimidazole with methanol. Other 5 - hydrocarbonoxy - thiocarbonylamino substituents may be added merely by using an appropriate alcohol.

25 The 5 - hydrocarbonthio - thiocarbonyl - amino benzimidazoles of this invention may be prepared by reacting a 5 - isothiocyanato benzimidazole with a thiol. The reaction may be carried out by reacting the 5 - isothio-

30 cyanato benzimidazole in a suitable organic solvent at room temperature with the thiol. Reaction is usually complete in from about 10 to about 24 hours after which the product is precipitated from the reaction mixture

35 by the addition of water. The product is recovered by filtration, purified by conventional recrystallization techniques. Thus, for example, 5 - methylthio - thiocarbonylamino - 2 - (4' - thiazolyl)benzimidazole is prepared by treat-

40 ing 5 - isocyanato - 2 - (4' - thiazolyl) - benzimidazole with methyl thiol. To prepare the other 5 - hydrocarbonthio - thiocarbonyl - amino benzimidazoles of this invention, it is merely necessary to select the appropriate

45 thiol.

The 5 - thiocarbonylamino benzimidazoles of this invention are readily prepared from the corresponding 5 - carbonylamino benzimidazoles by treating the 5 - carbonyl -

50 amino benzimidazole at reflux in a suitable organic solvent such as pyridine with phosphorus pentasulfide. Upon completion of the reaction, which usually requires about 20 to about 40 minutes, the reaction mixture is

55 poured onto ice and the product which separates is recovered by filtration and purified by conventional techniques.

The 5 - carbonylamino benzimidazoles of this invention in which R_4 is a C_{1-8} alkyl -

60 amino radical may be prepared by treating a 5 - amino - 2 - R_1 benzimidazole at room temperature in a suitable organic solvent such as pyridine with a C_{1-8} alkyl isocyanate. Reaction is usually complete in about 2 to 4

65 hours, after which the product is precipitated

from the reaction mixture by the addition of water and is recovered by filtration. Purification is achieved by conventional recrystallization techniques.

5 - Di(C_{1-8} alkyl)amino - carbonylamino benzimidazoles can be prepared by reacting a 5 - amino - 2 - R_1 benzimidazole at room temperature in an organic solvent such as pyridine with a di(C_{1-8} alkyl)carbonyl halide, preferably the carbonyl chloride. The reaction is usually complete in about 1 to 3 hours, after which the product is recovered and purified by the techniques previously described.

Alternatively, 5 - di(C_{1-8} alkyl)amino - carbonylamino benzimidazoles can be prepared from a corresponding 5 - alkylthiolcarbonyl - amino benzimidazole by refluxing a mixture of the 5 - alkylthiolcarbonylamino benzimidazole and a di(C_{1-8} alkyl)amine. After refluxing for about 1 to 2 hours, the reaction mixture is evaporated and water is added to precipitate the product which is recovered and purified by conventional techniques. This reaction also may be used to prepared 5 - (cyclic alkylenimino or hetero-interrupted alkylenimino) - carbonylamino benzimidazoles in which case a cyclic alkylenimine or hetero-interrupted alkylenimine is used instead of the di(C_{1-8} alkyl) amine.

The 5 - thiocarbonylamino benzimidazoles of this invention, in which R_4 is a C_{1-8} alkylamino radical may be prepared by reacting a 5 - amino - 2 - R_1 - benzimidazole at room temperature in an organic solvent such as pyridine with C_{1-8} alkyl isothiocyanate. The reaction usually requires about 1 to 3 hours for completion. The product is precipitated from the reaction mixture by adding water and is recovered by filtration and purified by conventional recrystallization techniques.

5 - Di(C_{1-8} alkyl)amino - thiocarbonylamino and (cyclic alkylenimino and hetero-interrupted alkylenimino) - thiocarbonyl amino benzimidazoles may be prepared by reacting a 5 - isothiocyanato benzimidazole with a di(C_{1-8} alkyl)amine or a cyclic alkylenimine or hetero-interrupted alkylenimine. The reaction may be carried out in the presence of water or an alcoholic solvent. Although the reaction will proceed at room temperature, it may also be carried out at reflux temperatures. The reaction is usually complete in about 1 to 6 hours, after which the solid product, if not already separated from the reaction mixture, may be precipitated by the addition of water. The crude product is recovered and purified by conventional techniques.

The 1 - substituted benzimidazoles of this invention, in which R_2 is hydroxy, C_{1-8} alkoxy, carboxyalkoxy, C_{1-8} alkyl, aralkyl and acyl are normally prepared from the parent benzimidazoles by well known techniques (see, for example, U.S. Patents 3,017,415;

3,080,282; 3,183,239 and 3,265,706 and Belgian Patent 674,202). Alternatively, however, the 1 - substituent may be added to a 2 - R_1 - benzimidazole by the known techniques and the resulting 1 - substituted - 2 - R_1 - benzimidazole may then be converted into the corresponding 1 - substituted - 5 - amino - 2 - R_1 benzimidazole by techniques hereinafter described. The 1 - substituted - 5 - amino - 2 - R_1 benzimidazoles, of course, may be used as intermediates in the various preparations described above in the same way as were the 5 - amino - 2 - R_1 benzimidazoles.

1 - Carbamoyl benzimidazoles of this invention are also prepared from the corresponding 1 - unsubstituted benzimidazoles by treating the parent benzimidazole with an isocyanate in a suitable organic solvent such as acetonitrile. Thus, 1 - n - butylcarbamoyl - 5 - isopropylcarbonylamino - 2 - (4' - thiazolyl)benzimidazole is prepared by treating 5 - isopropoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole with n - butyl isocyanate. The reaction is carried out at reflux temperature and is usually complete in about 2 to 6 hours. The product is recovered by extracting the reaction mixture with chloroform and is isolated by chromatography of the chloroform extract through silica gel.

Benzimidazoles of this invention having an alkoxycarbonyl radical at the 1-position are prepared by treating the corresponding 1 - unsubstituted benzimidazoles with an alkyl haloformate, preferably a chloroformate. This reaction is carried out in substantially the same manner as that heretofore described for preparation of the 5 - carbamate species. Because of the tautomeric nature of the benzimidazole nucleus, there will be formed also some 1,6 - disubstituted benzimidazole in the foregoing preparations.

Benzimidazoles of the invention having a C_{1-8} alkyl, an aralkyl or an acyl radical at the 1 - position are prepared by treating an alkali metal salt of the corresponding 1 - unsubstituted compound with a C_{1-8} alkyl halide, an aralkyl halide or an acyl halide.

In the specification of our copending application No 46573/69 (Serial No. 1,198,942) there are claimed 2 - R_1 - benzimidazoles (where R_1 is as previously defined) having at the 5 - position an alkyl or aryl sulfonyl - amino substituent, examples of such compounds being those wherein the 5 - substituent is methylsulfonylamino, ethylsulfonylamino, phenylsulfonylamino and tolylsulfonylamino. These compounds are obtained as described and claimed in the said copending application, by reaction of the appropriate 2 - R_1 - amino benzimidazole with an alkyl or aryl sulfonyl halide, and preferably an alkyl or aryl sulfonyl chloride. In addition to having anthelmintic activity *per se*, these compounds serve as valuable intermediates in the prepara-

tion of the benzimidazoles of the present invention, in which the R_2 substituent is a C_{1-8} alkyl radical.

In accordance with the invention claimed in said copending application, the 5 - (alkyl or aryl) sulfonylamino benzimidazoles are converted into the corresponding N - alkyl 5 - (alkyl or aryl) sulfonylamino benzimidazole by treatment with an alkyl halide in an organic solvent such as methanol. The reaction is carried out in the presence of an alkali metal alkoxide such as sodium methoxide, which serves as an acid-binding agent. The 5 - N - alkyl - (alkyl or aryl) - sulfonylamino benzimidazoles so produced then may be converted into the corresponding 5 - alkylamino benzimidazoles by refluxing in a concentrated mineral acid such as concentrated hydrochloric acid. These 5 - alkylamino benzimidazoles are then used as intermediates in the various preparations described above in the same way as were the 5 - amino benzimidazoles.

As stated previously, the compounds of Formula I above have significant activity as anthelmintics. The disease or group of diseases described generally as helminthiasis is due to infestation of the animal body with parasitic worms known as helminths. Helminthiasis is a prevalent and serious economic problem in domesticated animals such as swine, sheep, cattle, goats, dogs and poultry. Among the helminths, the group of worms described as nematodes causes widespread and oftentimes serious infection in various species of animals. The most common genera of nematodes infecting the animals referred to above are *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Bunostomum*, *Oesophagostomum*, *Chabertia*, *Trichuris* (whipworm), *Ascaris*, *Capillaria*, *Heterakis* and *Ancylostoma*. Certain of these, such as *Trichostrongylus*, *Nematodirus* and *Cooperia*, attack primarily the intestinal tract while others, such as *Haemonchus* and *Ostertagia*, are more prevalent in the stomach. The parasitic infections known as helminthiasis lead to anemia, malnutrition, weakness, weight loss and severe damage to the walls of the intestinal tract and, if left untreated, often result in death of the infected animals. The benzimidazoles of this invention have unexpectedly high activity against these helminths. When used as anthelmintic agents they may be administered orally in a unit dosage form such as a capsule, bolus, tablet or as a liquid drench. The drench is normally an aqueous suspension or dispersion of the active ingredient together with a suspending agent such as bentonite and a wetting agent or like recipient. Generally, the drenches also contain an antifoaming agent. The capsules and boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate, or dicalcium phosphate. When the anthelmintic is to be ad-

ministered in the animal feedstuff, it is intimately dispersed in the feed or else used as a top dressing or in the form of pellets which are then added to the finished feed. Alternatively, the anthelmintics of the invention may be administered to animals by intraruminal, intramuscular and intratracheal injection, in which event the benzimidazole is dissolved or dispersed in a liquid carrier vehicle.

Although the anthelmintic agents of this invention find their primary use in the treatment and/or prevention of helminthiasis in domesticated animals, such as sheep, cattle, horses, dogs, swine and goats, they are also effective in treatment of helminthiasis that occurs in other living animals. The optimum amount to be used will, of course, depend upon the particular benzimidazole, the species of animal and the type and severity of helminth infection. Generally, good results are obtained with compounds of the present invention by the oral administration of from about 5 to 125 mg. per kg. of animal body weight, such total dose being given at one time or in divided doses over a relatively short period of time such as 1—2 days. With the preferred compounds of the invention, excellent control of helminthiasis is obtained in domesticated animals by administering from about 10 to 70 mg. per kg. of body weight in a single dose. The techniques for administering these materials to animals are known to those skilled in the veterinary field.

Certain of the 2 - R₁ - 5 - amino benzimidazoles used as starting materials in the processes of our invention have been reported in the literature. These, as well as those which have not been specifically described, may be prepared from the 2 - R₁ - benzimidazole unsubstituted at the 5 - position (wherein R₁ is as previously defined) by reaction of such an 5 - unsubstituted compound with nitric acid in the presence of sulfuric acid, which gives essentially selective nitration at the 5 - position and thus affords the corresponding 2 - R₁ - 5 - nitrobenzimidazole. This latter substance is then conveniently reduced to the 5 - amino compound by catalytic hydrogenation in the presence of palladium-on-charcoal catalyst. Details of these procedures, as well as alternative procedures, are set forth below.

Preparation of 5-Nitro Benzimidazoles

A.) 5 - Nitro - 2 - (4' - thiazolyl) - Benzimidazole:

10 g. of 2 - (4' - thiazolyl)benzimidazole is dissolved with cooling in 20 ml. of concentrated sulfuric acid. To this solution is added dropwise with cooling and stirring a mixture of 4 ml. of concentrated nitric acid and 6 ml. of concentrated sulfuric acid, maintaining the temperature between 20° and 30°C. The reaction mixture is allowed to

stir for a further five minutes at room temperature then poured onto ice and made just basic with ammonium hydroxide. The solid 5 - nitro - 2 - (4' - thiazolyl)benzimidazole is filtered off and washed with water. It is recrystallized from dimethylformamide to give pale yellow needles of 5 - nitro - 2 - (4' - thiazolyl)benzimidazole, m.p. 240—241°C.

By employing equivalent molar quantities of benzimidazoles such as, 2 - [3' - (1',2',5' - thiadiazolyl)]benzimidazole, 2 - [4' - (1',2',3' - thiadiazolyl)]benzimidazole, 2 - [2' - (1',3',4' - thiadiazolyl)]benzimidazole, 2 - (1' - pyrazolyl)benzimidazole, 2 - (2' - methyl - 4' - thiazolyl)benzimidazole, 2 - (2' - oxazolyl)benzimidazole, 2 - (2' - thiazolyl)benzimidazole, or 2 - (2' - imidazolyl)benzimidazole in the above procedure in place of the 2 - (4' - thiazolyl)benzimidazole, there is obtained the corresponding 5 - nitro derivative.

The foregoing nitration procedure is highly satisfactory for those compounds in which the heteroaryl substituent at the 2 - position is not readily nitrated. In cases where the 2 - substituent may be nitrated as well as the 5 - position of the benzimidazole ring, an alternative synthesis of the 2 - R₁ - 5 - amino benzimidazoles is used which comprises the reaction of *o* - amino - *p* - nitro - aniline with a heteroaryl aldehyde in the presence of nitrobenzene or cupric diacetate. This method is illustrated below.

B.) 5 - Nitro - 2 - (2' - furyl)Benzimidazole

2.2 g. of 2 - furfuryl aldehyde in 3 ml. of ethanol is added to a suspension of 3 g. of *o* - amino - *p* - nitroaniline in 10 ml. of nitrobenzene. The resulting mixture is stirred for 10 minutes at room temperature and then heated slowly to 210°C. For one minute. The methanol is allowed to distil during this heating. The mixture is then cooled to about 5°C. to crystallize the 5 - nitro - 2 - (2' - furyl)benzimidazole which is recovered by known methods, m.p. 224°C.

C.) 5 - Nitro - 2 - (2' - pyrrol)Benzimidazole

43.2 g. of pyrrole - 2 - aldehyde in methanol is added to a suspension of 54.0 g. of *o* - amino - *p* - nitroaniline and 160 g. of cupric diacetate in methanol (total of 1 liter) and this mixture is then heated at reflux temperature for 2 hours. The mixture is cooled to room temperature and the copper complex of the product is removed by filtration and suspended in ethanol and then treated with gaseous hydrogen sulfide to give 5 - nitro - 2 - (2' - pyrrol)benzimidazole, m.p. 259—260°C.

By using an equivalent molar quantity of thiophene - 2 - aldehyde in the above reaction in place of the pyrrole - 2 - aldehyde,

POOR QUALITY

there is obtained 5 - nitro - 2 - (2' - thienyl) - benzimidazole.

Preparation of 5 - Amino Benzimidazoles

5 - Amino - 2 - (4' - thiazolyl)Benzimidazole:

- 5 A suspension of 141 g. of 5 - nitro - 2 - (4' - thiazolyl)benzimidazole in 4 liters of dry ethanol is reduced with 22 g. of 5%, palladium-on-carbon catalyst and hydrogen at 24°C. and 45 psi. The theoretical amount of
- 10 hydrogen is absorbed in approximately 5½ hours. The catalyst is then filtered off and the solvent evaporated to near dryness. The solid is recovered by filtration and washed with ether to afford 5 - amino - 2 - (4' -
- 15 thiazolyl)benzimidazole as a yellow solid. It is dissolved in absolute ethanol and crystallized by addition of hexane to give substantially pure material, m.p. 232—233°C.

- 20 By using equivalent molar quantities of the 5 - nitro - 2 - R₁ benzimidazole prepared as described in the foregoing section in the above procedure instead of the 5 - nitro - 2 - (4' - thiazolyl)benzimidazole, corresponding 5 - amino - 2 - R₁ benzimidazoles are obtained.

The foregoing methods for making 2 - R₁ - 5 - amino benzimidazoles are not a part of the present invention.

- 30 Most of the haloformate, halothioformates and acyl halides used as the second reactant in the process of the invention are known; those not specifically reported in the literature are prepared by known methods.

- 35 The following Examples are given for the purpose of illustration of the present invention. Example 75 and Steps A and B of Example 76 illustrate the invention claimed in the specification of our copending application No. 46573/69 (Serial No. 1,198,942), but
- 40 are included herein for the sake of completeness.

EXAMPLE 1

5 - Methoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 45 To a suspension of 2.16 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 7.5 ml. of pyridine there is added dropwise with stirring 1 g. (0.815 ml.) of methyl chloroformate. The mixture is stirred for a further two hours
- 50 at room temperature and then several volumes of ice and water are added to precipitate the product. The solid thus obtained is collected by filtration and washed with water to give 5 - methoxy - carbonylamino - 2 -
- 55 (4' - thiazolyl)benzimidazole, m.p. 225—226°C. It is dissolved in methanol and the solution is treated with decolorizing charcoal and then evaporated to near dryness. 5 - Methoxycarbonylamino - 2 - (4' - thiazolyl) -
- 60 benzimidazole crystallizes and is recovered by filtration and dried *in vacuo* for two hours at 65°C. to afford pure material, m.p. 237—239°C.

EXAMPLE 2

5 - Methoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 3.86 g. of methyl chloroformate in 100 ml. of acetone is added at room temperature to a stirred solution of 10.2 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 300 ml. of acetone, and the resulting mixture is stirred for one hour at room temperature. At the end of this time the solid product is collected by filtration, washed with acetone and dissolved in water. The aqueous solution is made basic with sodium bicarbonate and the resulting precipitate filtered off and washed with water. The solid is dissolved in a minimum volume of hot methanol, the methanolic solution treated with decolorizing charcoal and filtered, and the methanolic filtrate is evaporated to a small volume. 5 - Methoxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole crystallizes and is recovered by filtration, m.p. 220—222°C. The product is recrystallized from methanol and then dried for two hours *in vacuo* at 65°C. to give substantially pure 5 - methoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 234—235°C.

EXAMPLE 3

5 - Ethoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 2.27 g. of ethyl chloroformate is added dropwise over a 10 minute period to a stirred solution of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 15 ml. of pyridine. The resulting mixture is stirred for two hours at room temperature, then poured onto ice and diluted with water to a volume of about 300 ml. The resulting solid product is removed by filtration and washed with water. It is crystallized from a mixture of methanol, ether and petroleum ether, with a decolorizing-charcoal treatment of the solution, to give the methanol solvate of 5 - ethoxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 94—105°C.

- When the above reaction is repeated and the solid product that is recovered from the aqueous solution is recrystallized from acetonitrile - ether, there is obtained substantially pure 5 - ethoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 203—205°C.

EXAMPLE 4

5 - Propoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 2.60 g. of *n* - propyl chloroformate is added at room temperature to a stirred solution of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 15 ml. of pyridine. The resulting mixture is stirred at room temperature for 2 hours, then poured onto ice. The mixture is diluted with water to a volume of about 300 ml. A dark oil separates and is recovered by decanting the mother

liquors. The oil is washed with water and then dissolved in methanol. The methanolic solution is filtered and evaporated to near dryness *in vacuo*, and the residue is dried by adding benzene and removing the benzene by distillation. The residue is then crystallized from a mixture of methanol, ether and petroleum ether and the crystals are separated and air dried to give 5 - propoxycarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, m.p. 214—215°C.

EXAMPLE 5

5 - *n* - Butoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole is added to 15 ml. of pyridine, and to the resulting mixture there is added with stirring over a 10 minute period 2.9 g. of *n* - butyl chloroformate. The mixture is stirred for two hours at room temperature, then poured onto ice and diluted to 300 ml. with water. The resulting solid product is collected by filtration, washed with ice water and recrystallized from methanol to give substantially pure 5 - *n* - butoxycarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, m.p. 211—212°C.

EXAMPLE 6

5 - Amyloxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
When the procedure of Example 5 is repeated using 3.2 g. of *n* - amyl chloroformate instead of butyl chloroformate, there is obtained 5 - amyloxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 178—179°C.

EXAMPLE 7

5 - *n* - Hexyloxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
The procedure of Example 5 is repeated using 3.5 g. of *n* - hexyl chloroformate instead of butyl chloroformate. The 5 - *n* - hexyloxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole thus obtained melts at 150—152°C.

EXAMPLE 8

5 - *n* - Octyloxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
When the procedure of Example 5 is carried out replacing the butyl chloroformate of that example with 4.05 g. of *n* - octyl chloroformate, there is obtained 5 - *n* - octyloxycarbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 66—67°C.

EXAMPLE 9

5 - Phenoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
3.5 g. of phenyl chloroformate is added dropwise over 10 minutes to a mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 18 ml. of dry pyridine.

There is an exothermic reaction and the temperature rises to about 60°C. The mixture is cooled to about room temperature, stirred for about two hours, and diluted with water to a volume of 500 ml. The container is scratched to induce crystallization and the resulting crystals are collected, washed with cold water and dried to give 5 - phenoxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole.

This material is dissolved in a minimum volume of methanol, the solution treated with decolorizing charcoal and concentrated to a small volume. About 1/10 volume of ether is added and the resulting solid product collected by filtration and dried *in vacuo* to afford 5 - phenoxy carbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 115—116°C.

EXAMPLE 10

5 - *p* - Fluorophenoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
Employing the process of Example 9 using 4.63 g. of *p* - fluorophenylchloroformate instead of the phenyl chloroformate, there is obtained 5 - *p* - fluorophenoxycarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, m.p. 275—280°C.

EXAMPLE 11

5 - *o* - Fluorophenoxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
4.63 g. of *o* - fluorophenyl chloroformate were added dropwise to a mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 35 ml. of dimethyl formamide. After 2½ hours, 500 ml. of ether is added and the powder which separates is collected and treated with aqueous ammonia yielding 5 - *o* - fluorophenoxycarbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 135—140°C.

EXAMPLE 12

5 - Isobutyloxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole
2.9 g. of isobutyl chloroformate is added dropwise to a mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 20 ml. of dry pyridine, the addition being carried out at room temperature. The mixture is stirred at room temperature for 90 minutes and then about 200 ml. of ice water is added. The resulting solid is collected by filtration and washed with water. It is dissolved in a minimum volume of methanol and the methanolic solution treated with decolorizing charcoal. The charcoal is filtered off and the clear solution evaporated to a small volume and a small amount of water added to induce crystallization. 5 - Isobutyloxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole crystallizes and is separated and dried, m.p. 231—232°C.

EXAMPLE 13

5 - Isopropoxy carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 5 The procedure of Example 12 is repeated using 2.6 g. of isopropyl chloroformate. There is obtained 2 - isopropoxy carbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 212—214°C.

EXAMPLE 14

10 5 - Allyloxy carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 15 The procedure of Example 12 is repeated using 3.12 g. of allyl chloroformate in place of isobutyl chloroformate to afford 5 - allyloxy carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 210—212°C.

EXAMPLE 15

20 5 - (2 - Propynyl) - oxycarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 25 When the procedure of Example 12 is repeated using 2.61 g. of 2 - propynyl chloroformate in place of isobutyl chloroformate there is obtained 5 - (2 - propynyl) - oxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 200—202°C.

EXAMPLE 16

30 5 - Ethylthiocarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 35 25.3 g. of ethyl chlorothioformate is added dropwise to a stirred suspension of 40 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 150 ml. of pyridine. The mixture is stirred for 4 hours and a mixture of ice and water is added to precipitate 5 - ethylthiocarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole, m.p. 215°C.

EXAMPLE 17

40 5 - Cyclopropoxy carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

- 45 A mixture of 1.1 g. of 5 - ethylthio - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole and 0.15 g. of dibutyltin oxide in 1.5 g. of cyclopropanol is refluxed for 20 hours. The solvent is evaporated and the residue is crystallized from a mixture of ethyl acetate and hexane to give 5 - cyclopropoxy - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 190—195°C. (hydrate), 2.7—208°C. (anhydrous).

EXAMPLE 18

50 5 - Acetamido - 2 - (4' - Thiazolyl) - Benzimidazole

- 55 To a suspension of 6.48 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 23 ml. of pyridine there is added dropwise at room temperature over a 5—7 minute period 2.4 ml. of acetyl chloride. The resulting mixture is stirred for two hours at room temperature, and ice water then added to a volume of about 200 ml. The solid product is recovered

by filtration, washed with water and dried *in vacuo* for 18 hours to give crude 5 - acetamido - 2 - (4' - thiazolyl)benzimidazole, m.p. 240—250°C. This product is dissolved in methanol and the solution is treated with decolorizing charcoal, filtered and then concentrated to the point of crystallization. It is chilled and the crystals are collected, washed with methanol and dried *in vacuo* to afford substantially pure product, m.p. 260°C.

EXAMPLE 19

5 - Phenylacetamido - 2 - (4' - Thiazolyl) - Benzimidazole

To a mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 18 ml. of dry pyridine there is added slowly over a 10-minute period of room temperature 3 ml. of phenylacetyl chloride. The mixture is stirred at room temperature for two hours and then the product recovered as in Example 18 to afford 5 - phenylacetamido - 2 - (4' - thiazolyl)benzimidazole, m.p. 210—211°C.

EXAMPLE 20

5 - Formylamino - 2 - (4' - Thiazolyl) - Benzimidazole

4 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole is mixed with 300 ml. of 99% formic acid, and the resulting mixture is stirred at room temperature for 20 hours. At the end of this time, about 300 ml. of ice water is added and the mixture brought to pH 8 with concentrated aqueous ammonium hydroxide. The resulting solid precipitate is separated by filtration and dried to give crude 5 - formylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 242—244°C. This material is purified by dissolving it in methanol, treating with decolorizing charcoal, filtering, and concentrating until crystallization begins. The resulting pure material melts at 247—248°C.

EXAMPLE 21

5 - Propionamido - 2 - (4' - Thiazolyl) - Benzimidazole

To a mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole and 20 ml. of pyridine there is added dropwise 1.85 g. of propionyl chloride. The reaction mixture is stirred for one hour at room temperature and water is then added to the point of cloudiness. The mixture is chilled and the solid product recovered. The solid crystallizes by dissolving in methanol and then evaporating the methanol solution to a small volume. 5 - Propionamido - 2 - (4' - thiazolyl)benzimidazole crystallizes and is recovered by filtration, m.p. 255—256°C.

EXAMPLE 22

5 - Benzamido - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 21 is

repeated using 2.81 g. of benzoyl chloride in place of propionyl chloride, there is obtained 5 - benzamido - 2 - (4' - thiazolyl) - benzimidazole, m.p. 118—120°C.

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EXAMPLE 23

5 - Nicotinylamino - 2 - (4' - Thiazolyl) - Benzimidazole

4.56 g. of nicotinic anhydride is added slowly to 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 20 ml. of pyridine. The resulting mixture is stirred until the solids are dissolved and then allowed to stand at room temperature for 20 hours. An equal volume of water is then added and the resulting solid product collected by filtration and washed with water. It melts at 282—284°C. This material is dissolved in dimethyl formamide and water is added to induce crystallization. The resulting crystals are collected, washed with methanol and ether and dried to afford substantially pure 5 - nicotinylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 284—285°C.

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EXAMPLE 24

5 - *o* - Fluorobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

When the procedure of Example 23 is repeated using 5.24 g. of *o* - fluorobenzoic anhydride in place of nicotinic anhydride, the resulting crude product crystallized from aqueous methanol, there is obtained substantially pure 5 - *o* - fluorobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 132—133°C.

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EXAMPLE 25

5 - (1 - Adamantanyl)Carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

When the procedure of Example 22 is carried out using 3.97 g. of adamantane - 1 - carbonyl chloride in place of benzoyl chloride, 5 - (1 - adamantanyl)carbonylamino - 2 - (4' - thiazolyl)benzimidazole is produced, m.p. 246—247°C.

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EXAMPLE 26

5 - (2 - Naphthoylamino) - 2 - (4' - Thiazolyl)Benzimidazole

The procedure of Example 22 is repeated using 4 g. of 2 - naphthoyl chloride in place of benzoyl, there is obtained in this manner 5 - (2 - naphthoylamino) - 2 - (4' - thiazolyl)benzimidazole, m.p. 154—156°C.

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EXAMPLE 27

5 - Cyclopropylcarbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 2.3 g. of cyclopropylcarbonyl chloride there is obtained 5 - cyclopropyl - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 245°C.

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EXAMPLE 28

5 - Isobutyrylamino - 2 - (4' - Thiazolyl) - Benzimidazole

Following the procedure of Example 21 and substituting 2.34 g. of isobutyryl chloride for the propionyl chloride, there is obtained 5 - isobutyrylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 203—205°C.

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EXAMPLE 29

5 - (3 - Thienyl)carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.21 g. of thiophene - 3 - carbonyl chloride for the propionyl chloride, there is obtained 5 - (3 - thienyl)carbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 276—278°C.

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EXAMPLE 30

5 - *m* - Fluorobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.4 g. of *m* - fluorobenzoyl chloride for the propionyl chloride, there is obtained 5 - *m* - fluorobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 232—233°C.

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EXAMPLE 31

5 - *p* - Fluorobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.4 g. of *p* - fluorobenzoyl chloride for the propionyl chloride, there is obtained 5 - *p* - fluorobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 151—152°C.

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EXAMPLE 32

5 - *o* - Methoxybenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.6 g. of *o* - methoxybenzoyl chloride for the propionyl chloride, there is obtained 5 - *o* - methoxybenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 113—114°C.

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EXAMPLE 33

5 - *m* - Methoxybenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.75 g. of *m* - methoxybenzoyl chloride for the propionyl chloride, there is obtained 5 - *m* - methoxybenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 105—109°C.

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EXAMPLE 34

5 - *o* - Phenoxybenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 4.87 g. of *o* - phenoxybenzoyl chloride for the propionyl chloride, there is

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obtained 5 - *o* - phenoxybenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 95—100°C.

EXAMPLE 35

- 5 5 - *o* - Chlorobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.68 g. of *o* - chlorobenzoyl chloride for the propionyl chloride, there is obtained 5 - *o* - chlorobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 146—147°C.

EXAMPLE 36

- 15 5 - *m* - Iodobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 7.2 g. of *m* - iodobenzoyl chloride for the propionyl chloride, there is obtained 5 - *m* - iodobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 127—129°C.

EXAMPLE 37

- 25 5 - *m* - Trifluoromethylbenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 4.22 g. of *m* - trifluoromethylbenzoyl chloride for the propionyl chloride, there is obtained 5 - *m* - trifluoromethylbenzoylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 201—203°C.

EXAMPLE 38

- 30 5 - *m* - Nitrobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.9 g. of *m* - nitrobenzoyl chloride for the propionyl chloride, there is obtained 5 - *m* - nitrobenzoylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 163—164°C.

EXAMPLE 39

- 40 5 - 2,5 - Difluorobenzoylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.9 g. of 2,5 - difluorobenzoyl chloride for the propionyl chloride, there is obtained 5 - (2,5 - difluorobenzoyl - amino) - 2 - (4' - thiazolyl)benzimidazole, m.p. 113—114°C.

EXAMPLE 40

- 50 5 - Picolinylamino - 2 - (4' - Thiazolyl) - Benzimidazole

Following the procedure of Example 21 and substituting 4.2 g. of picolinyl chloride hydrochloride for the propionyl chloride, there is obtained 5 - picolinylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 240—241°C.

EXAMPLE 41

- 55 5 - Isonicotinylamino - 2 - (4' - Thiazolyl) - Benzimidazole

Following the procedure of Example 21

and substituting 5 g. of isonicotinyl chloride hydrochloride for the propionyl chloride, there is obtained 5 - isonicotinylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 150—153°C.

EXAMPLE 42

- 65 5 - Pivaloylamino - 2 - (4' - Thiazolyl) - Benzimidazole

Following the procedure of Example 23 and substituting 4.10 g. of pivalic anhydride for the nicotinic anhydride, there is obtained 5 - pivaloylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 241—242°C.

EXAMPLE 43

- 75 5 - (2 - Furoyl)amino - 2 - (4' - Thiazolyl) - Benzimidazole

Following the procedure of Example 23 and substituting 4.4 g. of 2 - furoic anhydride for the nicotinic anhydride, there is obtained 5 - (2 - furoyl)amino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 139—140°C.

EXAMPLE 44

- 80 5 - (4' - Thiazolyl)Carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

The procedure of Example 21 is repeated using 3.1 g. of thiazole - 4 - carboxylic acid chloride in place of propionyl chloride to afford 5 - (4' - thiazolyl) - carbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 387—388°C.

EXAMPLE 45

- 90 5 - (2 - Thienyl) - Carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

When the procedure of Example 21 is repeated using 5 g. of thienoic acid anhydride in place of propionyl chloride there is obtained 5 - (2 - thienyl)carbonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 288°C. (d).

EXAMPLE 46

- 100 5 - Methoxyacetylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 2.3 g. of methoxyacetyl chloride for the propionyl chloride, there is obtained 5 - methoxyacetylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 238—239°C.

EXAMPLE 47

- 105 5 - Dichloroacetylamino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.68 g. of dichloroacetyl chloride for the propionyl chloride, there is obtained 5 - dichloroacetylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 220°C.

EXAMPLE 48

- 115 5 - (3,3 - Dimethylacryloyl)amino - 2 - (4' - Thiazolyl)Benzimidazole

Following the procedure of Example 21 and substituting 3.55 g. of 3,3 - dimethylacryloyl

chloride for the propionyl chloride, there is obtained 5 - (3,3 - dimethylacryloyl)amino - 2 - (4' - thiazolyl)benzimidazole, m.p. 270—272°C.

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EXAMPLE 49

5 - (2,2,2 - Trifluoroethoxy) - Carbonyl - amino - 2 - (4' - Thiazolyl)Benzimidazole

A mixture of 5 g. of 5 - ethylthiocarbonyl - amino - 2 - (4' - thiazolyl)benzimidazole and 10 0.5 g. of dibutyltin oxide in 50 ml. of 2,2,2 - trifluoroethanol is refluxed for 20 hours. The solvent is evaporated and the residue is crystallized from a mixture of ethyl acetate and hexane to give the title compound, m.p. 231—15 232°C.

EXAMPLE 50

5 - (2 - Propynyloxy) - Carbonylamino - 2 - (4' - Thiazolyl)Benzimidazole

When the procedure of Example 49 is 20 repeated employing 4 g. of the 5 - ethyl - thiocarbonylamino - 2 - (4' - thiazolyl) - benzimidazole, 0.4 g. of the dibutyltin oxide and substituting 25 ml. of 2 - propyn - 1 - ol for the 2,2,2 - trifluoroethanol, there is obtained 5 - (2 - propynyloxy)carbonylamino - 25 2 - (4' - thiazolyl)benzimidazole, m.p. 200—202°C.

EXAMPLE 51

5 - Phenoxythiocarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

3.62 g. of phenoxythiocarbonyl chloride is added dropwise to a stirred suspension of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 25 ml. of pyridine. After 35 stirring for 1.5 hours, water is added, and the solid which separates is collected and crystallized from methanol to give the title compound, m.p. 155—157°C.

EXAMPLE 52

40 5 - Isothiocyanato - 2 - (4' - Thiazolyl) - Benzimidazole

7.2 g. of 5 - phenoxythiocarbonylamino - 2 - (4' - thiazolyl) - benzimidazole is dissolved in 50 ml. of pyridine and heated for 45 one hour at 100°C. Addition of water to the solution precipitates 5 - isothiocyanato - 2 - (4' - thiazolyl) - benzimidazole, m.p. 243—246°C.

EXAMPLE 53

50 5 - Methoxythiocarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

A solution of 2.5 g. of 5 - isothiocyanato - 2 - (4' - thiazolyl) - benzimidazole and 25 mg. of sodium methoxide in 300 ml. of 55 methanol is refluxed for 20 hours. Evaporation of the solvent followed by recrystallization of the residue from methanol gives 5 - methoxy - thiocarbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 224°C.

EXAMPLE 54

5 - Ethoxythiocarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 53 is repeated using ethanol in place of methanol, the title compound is obtained, m.p. 218°C.

EXAMPLE 55

5 - Methylthiothiocarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

A slow stream of methyl mercaptan is passed into a solution of 4 g. of 5 - iso - thiocyanato - 2 - (4' - thiazolyl) - benzimidazole in 25 ml. of dimethylformamide for 15 minutes. The solution is allowed to stand at room temperature for twenty hours and then water is added to precipitate 5 - methylthiothiocarbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 202—205°C.

EXAMPLE 56

5 - Thiobenzoylamino - 2 - (4' - Thiazolyl) Benzimidazole

A mixture of 1 g. of 5 - benzoylamino - 2 - (4' - thiazolyl) - benzimidazole, 2 g. of phosphorus pentasulfide and 20 ml. of pyridine is refluxed for 25 minutes. The solution is poured onto ice and the product which separates is purified by column chromatography through silica using chloroform as the eluent. Crystallization from methanol gives the title compound, m.p. 140—143°C.

EXAMPLE 57

5 - (3 - Methylureido) - 2 - (4' - Thiazolyl) - Benzimidazole

1.2 g. of methyl isocyanate is added dropwise with stirring to a suspension of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 25 ml. of pyridine. After stirring for 2.5 hours, water is added and the solid which separates is filtered off and crystallized from methanol to give 5 - (3 - methylureido) - 2 - (4' - thiazolyl) - benzimidazole, m.p. 160°C.

EXAMPLE 58

5 - (3,3 - Dimethylureido) - 2 - (4' - Thiazolyl) - Benzimidazole

2.5 g. of dimethylcarbamoyl chloride is added dropwise with stirring to a suspension of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 25 ml. of pyridine. After stirring for 1.5 hours, water is added, and the solid which separates is collected and crystallized from methanol to give the title compound, m.p. 260—262°C.

EXAMPLE 59

5 - (3,3 - Diethylureido) - 2 - (4' - Thiazolyl) - Benzimidazole

A mixture of 5 g. of 5 - ethylthiocarbonyl - amino - 2 - (4' - thiazolyl) - benzimidazole and 25 ml. of diethylamine is refluxed for one hour. Evaporation to an oil followed

by addition of water precipitates a solid which is crystallized from chloroform to give 5 - (3,3 - diethylureido) - 2 - (4' - thiazolyl) - benzimidazole, m.p. 234—235°C.

5 EXAMPLE 60

5 - (1 - Pyrrolidinyl) - Carbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 59 is repeated using 25 ml. of pyrrolidine in place of diethylamine, the title compound is obtained, m.p. 296—298°C.

EXAMPLE 61

5 - (1 - Piperidinyl) - Carbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

15 When the procedure of Example 59 is repeated using 25 ml. of piperidine in place of diethylamine, the title compound is obtained.

EXAMPLE 62

20 5 - (3 - Methylthioureido) - 2 - (4' - Thiazolyl) - Benzimidazole

1.6 g. of methyl isothiocyanate is added dropwise with stirring to a suspension of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl) - benzimidazole in 25 ml. of pyridine. After stirring for two hours, water is added to precipitate a solid which is collected and crystallized from a mixture of dimethylformamide and water to give 5 - (3 - methylthioureido) - 2 - (4' - thiazolyl) - benzimidazole, m.p. 235—247°C.

EXAMPLE 63

5 - (3 - Phenylthioureido) - 2 - (4' - Thiazolyl) - Benzimidazole

35 When the procedure of Example 62 is repeated using 2.9 g. of phenyl isothiocyanate in place of methyl isothiocyanate, the title compound is obtained, m.p. 244—246°C.

EXAMPLE 64

40 5 - (3,3 - Dimethylthioureido) - 2 - (4' - Thiazolyl) - Benzimidazole

A mixture of 3 g. of 5 - isothiocyanato - 2 - (4' - thiazolyl) - Benzimidazole and 100 ml. of 40% aqueous dimethylamine is stirred at room temperature for five hours. The solid portion is collected and recrystallized from methanol to give the title compound, m.p. 156—159°C.

EXAMPLE 65

50 5 - (3,3 - Diethylthioureido) - 2 - (4' - Thiazolyl) - Benzimidazole

A solution of 4 g. of 5 - isothiocyanato - 2 - (4' - thiazolyl) - benzimidazole and 30 ml. of diethylamine in 50 ml. of ethanol is refluxed for one hour. Evaporation and addition of water gives a solid which is recrystallized from a mixture of methanol, ether and petroleum benzol to give 5 - (3,3 - diethylthioureido) - 2 - (4' - thiazolyl) - benzimidazole, m.p. 130—135°C.

EXAMPLE 66

5 - (piperidin - 1 - yl - thiocarbonylamino) - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 65 is repeated using 25 ml. of piperidine in place of the diethylamine (recrystallization of crude from a mixture of dimethylformamide and water), the title product is obtained, m.p. 225—226°C.

EXAMPLE 67

5 - (pyrrolidin - 1 - yl - thiocarbonylamino) - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 65 is repeated using 25 ml. of pyrrolidine in place of the diethylamine, the title compound is obtained, m.p. 257—258°C.

EXAMPLE 68

5 - Isopropoxycarbonylamino - 1 - Methyl - 2 - (4' - Thiazolyl) - Benzimidazole

To 8.5 g. of 5 - Isopropoxycarbonylamino - 2 - (4' - thiazolyl) - benzimidazole in 100 ml. of dry dimethylformamide is added 2.3 g. of a 52% sodium hydroxide emulsion in mineral oil. The mixture is stirred at room temperature for about twenty minutes and then warmed carefully to about 50°C. for ten minutes. It is cooled to room temperature and 7.1 g. of methyl iodide in 10 ml. of dimethylformamide is added slowly to the cooled solution. The reaction mixture is then heated to about 80°C. for 20 minutes, cooled, diluted with 200 ml. of water and extracted with three 100 ml. portions of ether. The ether extracts are combined, washed with water, dried over sodium sulfate, filtered, and the ether removed *in vacuo* to give the title compound which is purified by recrystallization from ethyl acetate.

By substituting equivalent quantities of propyl chloride, phenylethyl chloride, benzyl bromide, or isopropyl chloride for the methyl iodide in the above reaction, there are obtained, respectively, the corresponding 1 - propyl, 1 - phenethyl, 1 - benzyl and 1 - isopropyl benzimidazole.

EXAMPLE 69

5 - Isopropoxycarbonylamino - 1 - Methoxy - 2 - (4' - Thiazolyl) - Benzimidazole

A. 5 - Nitro - 1 - Methoxy - 2 - (4' - thiazolyl) - Benzimidazole

A mixture of 1.30 ml. of concentrated nitric acid (spg. 1.41) in 2.80 ml. of concentrated sulfuric acid (spg. 1.84) is added dropwise to a cold solution of 3.80 g. of 1 - methoxy - 2 - (4' - thiazolyl) - benzimidazole in 12.3 ml. of concentrated sulfuric acid. The reaction temperature is maintained at 12° ± 2° during addition by external cooling. The reaction mixture is stirred at room temperature for 30 minutes, then poured onto an ice water mixture. The pH of the suspension is adjusted to pH 8. The yellow solids

are collected by filtration and washed with water and cold methanol. Recrystallization from methanol yields 1.5 g. of purified product, m.p. 220-221°C.

5 B. 5 - Amino - 1 - Methoxy - 2 - (4' - Thiazolyl) - Benzimidazole .HCl

A suspension of 0.5 g. of 1 - methoxy - 2 - (4' - thiazolyl) - 5 - nitrobenzimidazole in 400 ml. of absolute ethanol is reduced using 1 g. of 10% palladium on carbon at room temperature in a hydrogen atmosphere at 40 lbs. p.s.i. When uptake of hydrogen is complete, the catalyst is removed by filtration and the filtrate is treated with 2.0 ml. of a 2.5N methanolic hydrogen chloride solution. The solvent is removed *in vacuo* to yield 450 mg. of amorphous product which is carried into the next step.

20 C. 5 - Isopropoxycarbonylamino - 1 - Methoxy - 2 - (4' - Thiazolyl) - Benzimidazole

A solution of the above hydrochloride salt in 15 ml. of pyridine is treated dropwise with 0.24 ml. of isopropyl chloroformate at room temperature. After stirring for 16 hours, the reaction mixture is diluted with 150 ml. of water and extracted with chloroform. The chloroform extracts are washed with water, dried over magnesium sulfate, filtered, and evaporated *in vacuo*. The oily residue is dissolved in chloroform and passed over a column of silica gel. Elution with a 5% methanol-95% chloroform mixture yields purified product. Recrystallization from ether-hexane mixture yields pure product, m.p. 123-125°C.

EXAMPLE 70

40 5 - Isopropoxycarbonylamino - 1 - Carboxy - methoxy - 2 - (4' - Thiazolyl) - Benzimidazole

When the procedure of Example 69 is repeated using 1 - carboxymethoxy - 2 - (4' - thiazolyl) - benzimidazole in step A in place of 1 - methoxy - 2 - (4' - thiazolyl) - benzimidazole, there is obtained the title compound.

EXAMPLE 71

50 5 - Isopropoxycarbonylamino - 1 - Hydroxy - (4' - Thiazolyl) - Benzimidazole

When the process of Example 69 is repeated using 1 - hydroxy - 2 - (4' - thiazolyl) - benzimidazole in place of 1 - methoxy - 2 - (4' - thiazolyl) - benzimidazole in Step A and carrying out the reduction of Step B in glacial acetic acid instead of absolute ethanol, the title product is obtained.

EXAMPLE 72

60 1 - Acetyl - 5 - Methoxycarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole

5.4 g. of 5 - methoxycarbonylamino - 2 -

(4' - thiazolyl) - benzimidazole is added to a mixture of 100 ml. of toluene and 30 ml. of dimethyl formamide. The mixture is distilled to remove 5 ml. of toluene and then 0.7 g. of sodium hydride in 2 ml. of toluene are added at about 65°C. The mixture is then stirred for one hour at this temperature and 2.5 g. of acetyl chloride added dropwise at 55°C. The resulting mixture is refluxed for 30 minutes, chilled and 2 ml. of water added to it. It is then washed with 5% aqueous sodium bicarbonate, filtered and evaporated to dryness *in vacuo* to afford a residue of 1 - acetyl - 5 - methoxycarbonylamino - 2 - (4' - thiazolyl) - benzimidazole.

Repeating this procedure with 3 g. of benzoyl chloride in place of the acetyl chloride affords 1 - benzoyl - 5 - methoxycarbonyl - amino - 2 - (4' - thiazolyl) - benzimidazole.

EXAMPLE 73

80 5 - Isopropoxycarbonylamino - 1 - Butyl - carbamoyl - 2 - (4' - Thiazolyl) - Benzimidazole

A solution of 3.26 g. of 5 - isopropyl - carbonylamino - 2 - (4' - thiazolyl) - benzimidazole and 1 g. of *n*-butyl isocyanate in 100 ml. of dry acetonitrile is refluxed for four hours. The solvent is evaporated and the residue is extracted with chloroform. The product is isolated by chromatography of the chloroform extract through silica gel.

Similarly, by using methyl isocyanate, ethyl isocyanate or propyl isocyanate in the above procedure in place of the butyl isocyanate, the corresponding methylcarbamoyl, ethylcarbamoyl and propylcarbamoyl analogs can be obtained.

EXAMPLE 74

100 5 - Isopropoxycarbonylamino - 1 - Iso - propoxycarbonyl - 2 - (4' - Thiazolyl) - Benzimidazole

2.6 g. of isopropyl chloroformate is added dropwise to a mixture of 4.5 g. of 5 - isopropoxycarbonylamino - 2 - (4' - thiazolyl) - benzimidazole in 20 ml. of dry pyridine, the addition being carried out at room temperature. The mixture is stirred at room temperature for another 90 minutes and then about 200 ml. of ice water are added. The resulting solid is separated by filtration and washed with water. It is dissolved in a minimum volume of methanol and the methanol solution is treated with decolorizing charcoal. The charcoal is filtered off and the clear solution is evaporated to a small volume. A small amount of water is added to induce crystallization. The product is separated and dried.

EXAMPLE 75

120 5 - Methylsulfonylamino - 2 - (4' - Thiazolyl)Benzimidazole

2.29 g. of methanesulfonyl chloride is

added dropwise at room temperature to a stirred mixture of 4.32 g. of 5 - amino - 2 - (4' - thiazolyl)benzimidazole in 20 ml. of pyridine. The mixture is then stirred for one hour and at the end of this time 100 ml. of water is added. The resulting solid product is separated and recrystallized twice from methanol to afford 5 - methylsulfonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 225—226°C.

When the procedure of above is repeated using 3.53 g. of benzenesulfonyl chloride, there is obtained 5 - benzenesulfonylamino - 2 - (4' - thiazolyl)benzimidazole, m.p. 254—255°C.

EXAMPLE 76

5 - N - Methylmethoxycarbonylamino - 2 - (4' - Thiazolyl) - Benzimidazole
A. 5 - N - Methylbenzenesulfonylamino - 2 - (4' - thiazolyl) - benzimidazole

0.625 ml. of methyl iodide is added to a mixture of 3.5 g. of 5 - benzenesulfonyl - amino - 2 - (4' - thiazolyl) - benzimidazole and 0.54 g. of sodium methoxide in 10 ml. of methanol. After 24 hours, water is added to precipitate a solid which is collected and crystallized from methanol to give 5 - N - methylbenzenesulfonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 142—143°C.

B. 5 - Methylamino - 2 - (4' - thiazolyl) - Benzimidazole

A solution of 4 g. of 5 - N - methyl - benzenesulfonylamino - 2 - (4' - thiazolyl) - benzimidazole in 100 ml. of concentrated hydrochloric acid is refluxed for 3 hours. evaporation of the excess of acid followed by basification gives a solid precipitate which is filtered off and crystallized for acetonitrile to give 5 - methylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 192—193°C.

C. 5 - N - Methylmethoxycarbonylamino - 2 - (4' - thiazolyl) - Benzimidazole

0.41 ml. of methyl chloroformate is added dropwise with stirring to a suspension of 1.15 g. of 5 - methylamino - 2 - (4' - thiazolyl) - benzimidazole in 5 ml. of pyridine. After stirring for 1 hour at room temperature water is added to precipitate a gum which is extracted with methylene chloride. Evaporation of the solvent followed by crystallization of the residue from a mixture of ether and petroleum benzene gives 5 - N - methyl - methoxycarbonylamino - 2 - (4' - thiazolyl) - benzimidazole, m.p. 161—162°C.

EXAMPLE 77

5 - Methoxycarbonylamino - 2 - (2' - Furyl) - Benzimidazole

Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - furyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title compound is obtained, m.p. 162—163°C.

EXAMPLE 78

5 - Methoxycarbonylamino - 1 - Methoxy - carbonyl - 2 - (2' - Furyl) Benzimidazole
Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 1 - methoxycarbonyl - 2 - (2' - furyl) benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) benzimidazole, the title compound is obtained, m.p. 164°C.

EXAMPLE 79

5 - Ethoxycarbonylamino - 2 - (2' - Furyl) Benzimidazole

Following the procedure of Example 3 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - furyl) Benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) benzimidazole, the title product is obtained, m.p. 171—172°C.

EXAMPLE 80

5 - Phenoxycarbonylamino - 2 - (2' -Furyl) Benzimidazole

Following the procedure of Example 9 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - furyl) benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) benzimidazole, the title product is obtained, m.p. 150—155°C.

EXAMPLE 81

5 - Ethoxycarbonylamino - 2 - (2' - Pyrrol) Benzimidazole

Following the procedure of Example 3 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - pyrrol) benzimidazole for the 5 - amino - 2 - (4' - thiazolyl)benzimidazole, there is obtained the title compound, m.p. 200—202°C.

EXAMPLE 82

5 - Methoxycarbonylamino - 2 - (2' - Thienyl) Benzimidazole

Following the procedure of Example 2 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - thienyl) benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, there is obtained the title compound, m.p. 185—188°C.

EXAMPLE 83

5 - Methoxycarbonylamino - 2 - [3' - (1',2',5' -Thiadiazolyl)] - benzimidazole

Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - [3' - (1',2',5' - thiadiazolyl)] - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title compound is obtained, m.p. 150—155°C.

EXAMPLE 84

5 - Methoxycarbonylamino - 2 - (1' - Pyrazolyl) Benzimidazole

Following the procedure of Example 1 and substituting an equivalent molar quantity of

5 - amino - 2 - (1' - pyrazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title compound is obtained, m.p. 207—210°C.

- 5 EXAMPLE 85
5 - Methoxycarbonylamino - 2 - (2' - Methyl - 4' - Thiazolyl) Benzimidazole
Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - methyl - 4' - thiazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title compound is obtained, m.p. 135°C.

- 15 EXAMPLE 86
5 - Methoxycarbonylamino - 2 - [4' - (1',2',3' - Thiadiazolyl)] - Benzimidazole
Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - [4' - (1',2',3' - thiadiazolyl)] - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title product is obtained, m.p. 218—220°C.

- 25 EXAMPLE 87
5 - Methoxycarbonylamino - 2 - [2' - (1',2',3' - Thiadiazolyl)] - Benzimidazole
Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - [2' - (1',2',3' - thiadiazolyl)] - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, the title product is obtained, m.p. 258°C.

- 35 EXAMPLE 88
5 - Isopropoxycarbonylamino - 2 - (2' - Oxazolyl) - Benzimidazole
Following the procedure of Example 1 and substituting equivalent molar quantities of 5 - amino - 2 - (2' - oxazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of isopropyl chloroformate for the methyl chloroformate, there is produced the title compound, m.p. 206°C.

- 45 EXAMPLE 89
5 - Isopropoxycarbonylamino - 2 - (2' - Thiazolyl) - Benzimidazole
Following the procedure of Example 1 and substituting equivalent molar quantities of 5 - amino - 2 - (2' - thiazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of isopropyl chloroformate for the methyl chloroformate, the title compound is obtained, m.p. 234°C.

- 55 EXAMPLE 90
5 - Methoxycarbonylamino - 2 - (2' - Imidazolyl) - Benzimidazole
Following the procedure of Example 1 and substituting an equivalent molar quantity of 5 - amino - 2 - (2' - imidazolyl) - benzimidazole for the 5 - amino - 2 - (4' -

thiazolyl) - benzimidazole, the title compound is obtained, m.p. 205—207°C.

- 60 EXAMPLE 91
5 - p - Fluorobenzoylamino - 2 - (2' - Furyl) - Benzimidazole
Following the procedure of Example 21 and substituting equivalent molar quantities of 5 - amino - 2 - (2' - furyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of p - fluorobenzoyl chloride for the propionyl chloride, the title compound is obtained, m.p. 264°C.

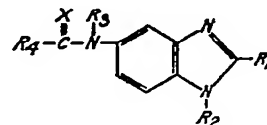
- 75 EXAMPLE 92
5 - (2 - Furyl) - Carbonylamino - 2 - (2' - Furyl) - Benzimidazole
Following the procedure of Example 21 and substituting equivalent molar quantities of 5 - amino - 2 - (2' - furyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of furyl - 2 - carbonyl chloride for the propionyl chloride, the title compound is obtained, m.p. 248°C.

- 85 EXAMPLE 93
5 - p - Fluorobenzoylamino - 2 - (1' - Pyrazolyl) - Benzimidazole
Following the procedure of Example 21 and substituting equivalent molar quantities of 5 - amino - 2 - (1' - pyrazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of p - fluoro - benzoyl chloride for the propionyl chloride, the title compound is obtained, m.p. 230°C.

- 95 EXAMPLE 94
5 - Benzoylamino - 2 - (2' - Thiazolyl) - Benzimidazole
Following the procedure of Example 21 and substituting equivalent molar quantities of 5 - amino - 2 - (2' - thiazolyl) - benzimidazole for the 5 - amino - 2 - (4' - thiazolyl) - benzimidazole, and of benzoyl chloride for the propionyl chloride, the title compound is obtained, m.p. 135—140°C.

WHAT WE CLAIM IS:—

1. A compound having the formula:



in which X represents an oxygen or sulfur atom; R₁ represents a five-membered monocyclic heteroaromatic ring containing from 1 to 3 of the following hetero atoms, viz., oxygen, sulfur and nitrogen; R₂ represents a hydrogen atom or a hydroxy, C₁₋₈ alkoxy, C₁₋₈ alkyl, aralkyl, acyl, acyloxy, carboxy- (C₁₋₈ alkoxy), carbamoyl, N-alkylcarbamoyl or alkoxy-carbonyl radical; R₃ represents a

- hydrogen atom or a C_{1-8} alkyl radical and R_4 represents a hydrogen atom, an aralkyl, haloaralkyl, cycloalkyl, C_{1-8} alkylamino, di- $(C_{1-8}$ alkyl)amino, cycloalkylamino, alkylenimino or hetero-interrupted alkylenimino radical, or a radical of formula $R-$, $RO-$ or $RS-$, in which R is a C_{1-8} univalent aliphatic hydrocarbon, C_{1-8} univalent aliphatic halohydrocarbon, aryl, heterocyclic, haloaryl, alkaryl or aminoaryl radical.

2. A non-toxic acid-addition salt or metal complex of a compound as claimed in claim 1, in which R_2 is a hydrogen atom.

3. A compound as claimed in claim 1 or 2, in which R_1 is a furyl, thienyl, pyrazolyl, imidazolyl, pyrrol, thiazolyl, thiadiazolyl, isothiazolyl or oxazolyl radical.

4. A compound as claimed in claim 3, in which X is oxygen and R_2 is hydrogen.

5. A compound as claimed in claim 4, in which R_1 is thiazolyl, R_2 is hydrogen and R_4 is a C_{1-8} alkoxy, benzoyl or *p*-fluorobenzoyl radical.

6. A 5 - (C_{1-8} alkoxy) - carbonylamino - 2 - (4' - thiazolyl)benzimidazole.

7. 5 - Methoxy - carbonylamino - 2 - (4' - thiazolyl)benzimidazole.

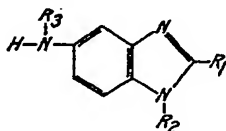
8. 5 - Ethoxy - carbonylamino - 2 - (4' - thiazolyl)benzimidazole.

9. 5 - Isopropoxy - carbonylamino - 2 - (4' - thiazolyl)benzimidazole.

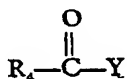
10. 5 - benzoylamino - 2 - (4' - thiazolyl) - benzimidazole.

11. 5 - *p* - Fluorobenzoylamino - 2 - (4' - thiazolyl)benzimidazole.

12. The process that comprises treating a compound of the formula:



in which R_1 , R_2 and R_3 are as defined in claim 1 with a compound of the formula:



in which Y is a halogen atom, and R_4 is a radical of formula $RO-$ or $RS-$ where R is as defined in claim 1, to produce a compound as claimed in claim 1 in which X is oxygen and R_4 is as defined above.

13. A process as claimed in claim 12 in which R_1 is as defined in claim 3 and R_2 is a hydrogen atom.

14. A process as claimed in claim 13, in which R_1 is a thiazolyl radical and R_4 is a C_{1-8} alkoxy radical.

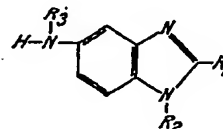
15. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with a C_{1-8} alkyl chloroformate to produce a compound as claimed in claim 6.

16. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with methyl chloroformate to produce the compound claimed in claim 7.

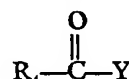
17. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with ethyl chloroformate to produce the compound claimed in claim 8.

18. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with isopropyl chloroformate to produce the compound claimed in claim 9.

19. The process that comprises treating a compound of the formula:



in which R_1 , R_2 and R_3 are as defined in claim 1, with a compound of the formula:



in which Y is a halogen atom and R_4 is a hydrogen atom, an aralkyl, haloaralkyl, cycloalkyl, C_{1-8} alkylamino, di- $(C_{1-8}$ alkyl)amino or cycloalkylamino radical, or a radical of formula $R-$ where R is as defined in claim 1, to produce a compound as claimed in claim 1 in which X is oxygen and R_4 is as defined above.

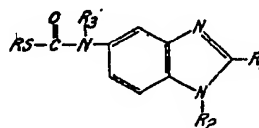
20. A process as claimed in claim 19, in which R_1 is as defined in claim 3 and R_2 is a hydrogen atom.

21. A process as claimed in claim 20, in which R_1 is a thiazolyl radical and R_4 is a benzyl or *p* - fluorobenzoyl radical.

22. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with benzoyl chloride to produce the compound claimed in claim 10.

23. The process that comprises reacting 5 - amino - 2 - (4' - thiazolyl) - benzimidazole with *p* - fluorobenzoyl chloride to produce the compound claimed in claim 11.

24. The process that comprises reacting a benzimidazole compound of the formula:



in which R , R_1 , R_2 and R_3 are as defined in claim 1 with a compound of the formula:

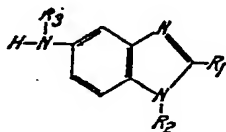


in which R is as defined in claim 1 but is not necessarily the same as R in the

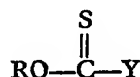
benzimidazole compound, in the presence of dibutyl tin oxide or aluminium isopropoxide to produce a compound as claimed in claim 1 in which X is oxygen and R₄ is a radical of formula RO— where R is as in the compound ROH.

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25. The process that comprises reacting a compound of the formula:

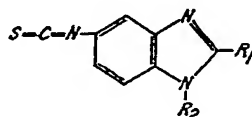


10 in which R₁, R₂ and R₃ are as defined in claim 1, with a compound of the formula:

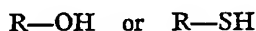


15 in which R is as defined in claim 1 and Y is a halogen atom, to produce a compound as claimed in claim 1 in which X is sulfur and R₄ is RO— where R is as defined in claim 1.

26. The process that comprises reacting a compound of the formula:

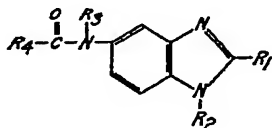


20 in which R₁ and R₂ are as defined in claim 1, with a compound of the formula:



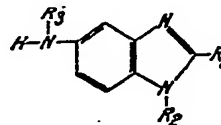
25 in which R is as defined in claim 1, to produce a compound as claimed in claim 1 in which X is sulfur and R₄ is RO— or RS— where R is as defined in claim 1.

27. The process that comprises reacting a compound of the formula:



30 in which R₁, R₂ and R₃ are as defined in claim 1 and R₄ is a hydrogen atom, an aralkyl, haloaralkyl, cycloalkyl, C₁₋₈ alkylamino, di-(C₁₋₈ alkyl)amino or cycloalkylamino radical, or a radical of formula R— where R is as defined in claim 1, with phosphorus pentasulfide to produce a compound as claimed in claim 1 in which X is sulfur and R₄ is as defined above.

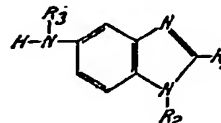
40 28. The process that comprises reacting a compound of the formula:



in which R₁, R₂ and R₃ are as defined in claim 1, with a C₁₋₈ alkyl isocyanate or a C₁₋₈ alkyl isothiocyanate, to produce a compound as claimed in claim 1 in which R₄ is C₁₋₈ alkylamino.

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29. The process that comprises reacting a compound of the formula:

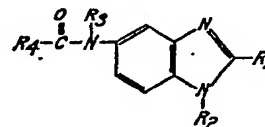


in which R₁, R₂ and R₃ are as defined in claim 1, with a di(C₁₋₈ alkyl)carbonyl halide to produce a compound as claimed in claim 1 in which X is oxygen and R₄ is di(C₁₋₈ alkyl)amino.

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30. The process that comprises reacting a compound of the formula:

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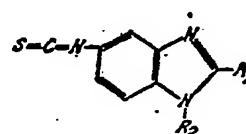


in which R₁, R₂ and R₃ are as defined in claim 1 and R₄ is C₁₋₈ alkylthio, with a di-(C₁₋₈ alkyl)amine or a cyclic alkylenimine or hetero-interrupted alkylenimine to produce a compound as claimed in claim 1 in which R₄ is a di(C₁₋₈ alkyl)amino or a cyclic alkylenimino or hetero-interrupted alkylenimino radical and X is oxygen.

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31. The process that comprises reacting a compound of the formula:

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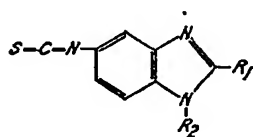
in which R₁ and R₂ are as defined in claim 1, with a di(C₁₋₈ alkyl)amine or a cyclic alkylenimine or hetero-interrupted alkylenimine to produce a compound as claimed in claim 1 in which R₄ is a di(C₁₋₈ alkyl)amino or a cyclic alkylenimino or hetero-interrupted alkylenimino radical and X is sulfur.

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32. The process that comprises heating a compound as claimed in claim 1 in which X is sulfur and R₄ is a radical of the formula RO—, where R is as defined in claim 1, with

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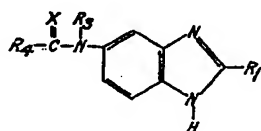
pyridine at about 100°C to produce a compound of the formula:



5 in which R₁ and R₂ are as defined in claim 1.

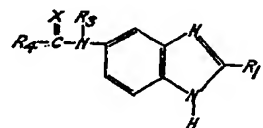
33. A process as claimed in claim 26 or 31, including the step of preparing the starting material by a process as claimed in claim 32.

10 34. The process that comprises treating an alkali metal salt of a compound having the formula:



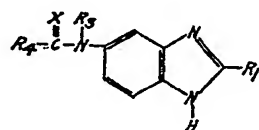
15 in which R₁, R₃, R₄ and X are as defined in claim 1, with a C₁₋₈ alkyl halide, an aralkyl halide or an acyl halide to produce a compound as claimed in claim 1 in which R₂ is a C₁₋₈ alkyl, aralkyl or acyl radical.

35. The process that comprises reacting a compound of the formula:



20 in which R₁, R₃, R₄ and X are as defined in claim 1, with an alkyl isocyanate to produce a compound as claimed in claim 1 in which R₂ is a carbamoyl radical.

25 36. The process that comprises reacting a compound of the formula:



30 in which R₁, R₃, R₄ and X are as defined in claim 1, with an alkyl haloformate to produce a compound as claimed in claim 1, in which R₂ is an alkoxycarbonyl radical.

37. A process as claimed in any one of claims 12, 19, 25, 28 and 29, including the step of preparing the starting material by a

process claimed in the specification of our 35 compending application No. 46573/69 (Serial No. 1,198,942).

38. A process as claimed in claim 24, including the step of preparing the starting material by a process as claimed in claim 12 or 13. 40

39. A process as claimed in claim 27 or 30, including the step of preparing the starting material by a process as claimed in any one of claims 19—23. 45

40. A process as claimed in claim 34, including the step of preparing the starting material by treating the product of a process as claimed in any one of claims 12—31 and 37—39 with a strong alkali metal base. 50

41. A process as claimed in claim 35 or 36, including the step of preparing the starting material by a process as claimed in any one of claims 12—31 and 37—39.

42. A process that produces a compound 55 as claimed in claim 1, substantially as hereinafore described in any one of Examples 1—74 and 76—94.

43. A compound as claimed in claim 1 or 2, when prepared by a process as claimed in any one of claims 12—42 or an obvious chemical equivalent of such a process. 60

44. An anthelmintic composition that comprises a carrier vehicle in which is intimately dispersed an anthelmintically effective amount of a compound as claimed in claim 1 or 2. 65

45. A composition as claimed in claim 44, in which the said compound is a compound as claimed in any one of claims 3—11 and 43. 70

46. An antifungal or anthelmintic composition comprising, as active ingredient, a compound as claimed in any one of claims 1—11 and 43, together with a non-toxic diluent, carrier or coating. 75

47. A composition as claimed in claim 46, in the form of a drench, tablet, bolus, capsule, animal feedstuff, pellet or injectable preparation. 80

48. A method for treating or preventing helminthiasis in non-human animals, that comprises administering to the animals a compound as claimed in any one of claims 1—11 and 43, whereby said helminthiasis is checked, cured or prevented. 85

49. A method as claimed in claim 48, in which the said compound is administered in the form of a composition as claimed in any one of claims 44—47.

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